Diborane Reduction of Penicillins: Preparation of 7-Deoxopenicillanic Acid

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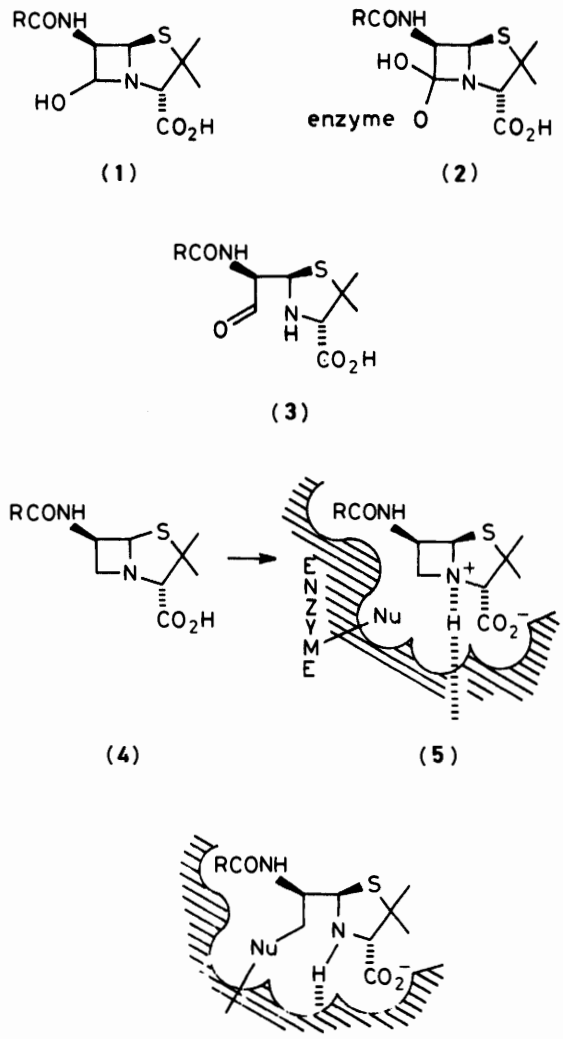
The reduction of 6β-acylamidopenicillanates with diborane is shown to proceed by opening of the β-lactam ring to produce the corresponding amino alcohols. The chemistry of the reduction product from benzhydryl 6β-benzyloxycarbonylaminopenicillanate has been explored, in particular its reaction with methanolic potassium hydroxide; no azetidines are formed. Cyclisation of the amino alcohol prepared from methyl penicillanate may be effected either indirectly, *via* the corresponding bromide, or directly, by use of a modified Mitsunobu reaction, to produce methyl 7-deoxypenicillanate.

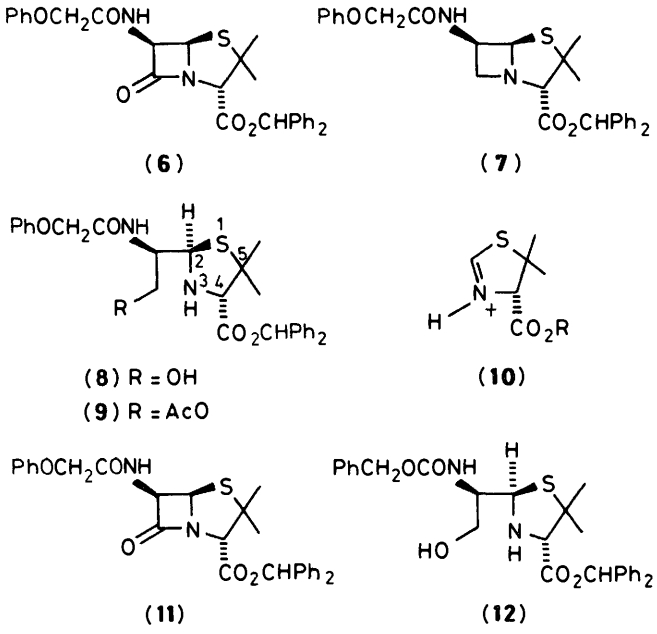
In the process of inhibiting bacterial cell-wall enzymes, β-lactam antibiotics such as penicillin have been described as transition-state analogues of natural substrates, such as R-D-Ala-D-Ala.[1] By comparison, some of the β-lactamases, a group of enzymes that can hydrolyse the β-lactam ring, treat these antibiotics as substrates.[2] The intriguing question then arises as to whether or not one can design transition-state analogues of the β-lactams themselves. A possible candidate is the alcohol (**1**), which would resemble the presumed orthoamide intermediate (**2**) found during β-lactamase attack on the β-lactam ring. Unfortunately, alcohols such as (**1**) are expected to be unstable, rapidly collapsing to the open aminoaldehyde (**3**). As a compromise candidate, therefore, we have considered the 7-deoxopenicillin (**4**). Although the 7-position bears no oxygen substituents, one might expect for this substance, compared with intermediates of the type (**2**), a more basic ring nitrogen atom allowing tighter bonding to any proton source in the active site. Furthermore, the protonated species (**5**) thus generated might behave as an alkylating agent for a functional group in the active site (Scheme 1); azetidinium species are known to have mild alkylating properties.[3]

Initially we used the reported synthesis of 7-deoxopenicillin G using a diborane reduction process.[4] Benzhydryl 6β-phenoxyacetamidopenicillanate (**6**), reduced under the conditions described by Nataraj *et al.*[4] afford, besides minor products, a more polar material lacking the β-lactam carbonyl absorption in its i.r. spectrum. The ^{1}H n.m.r. spectrum of this material showed extra protons at around δ 3.8, as expected for the replacement of the β-lactam carbonyl group by two hydrogens, and a mass spectrum showing an apparent parent ion at *m/z* 502, again suggesting the 7-deoxo compound (**7**). However, the high polarity of the product and the presence in the i.r. spectrum of strong absorptions between 3 000—3 600 cm^{-1} were more consistent with the plausible alternative structure, the amino alcohol (**8**); microanalysis of the reduction product indicated a molecular formula $C_{29}H_{32}N_2O_5S$, in agreement with structure (**8**). Chemical confirmation of the structure of the amino alcohol (**8**) was obtained by acetylation with acetic anhydride in pyridine, thus yielding a monoacetate (**9**). The broad n.m.r. signal at δ 3.6—3.9 in the starting alcohol (**8**) is shifted downfield to δ 4.2 on esterification, as expected upon acetylation of the alcohol group; the signals ascribed to the two protons adjacent to the thiazolidine nitrogen (3- and 5-H of the starting penicillanate), at δ 3.7 and 4.82 respectively, are not significantly shifted by the acetylation. The thiazolidine nitrogen is known to be rather unreactive and not readily acylated.[5] The mass spectral fragmentation patterns of the alcohol (**8**) and its acetate (**9**) supported these assignments; both showed efficient cleavage to give the thiazolinium ion (**10**; R = $CHPh_2$) as the base peak (*m/z* 326).



Scheme 1. Nu = nucleophile

Nataraj *et al.*[4] employed an *N*-protected penicillin bearing a 6β-benzyloxycarbonamide group, rather than a simple amide substituent associated with the penicillin V derivative (**6**). To ensure that this cleavage was not responsible for our different observations on the course of diborane reduction, the reaction was repeated using the benzyloxycarbonyl derivative (**11**). The amide (**11**) was prepared by the initial reaction of 6β-

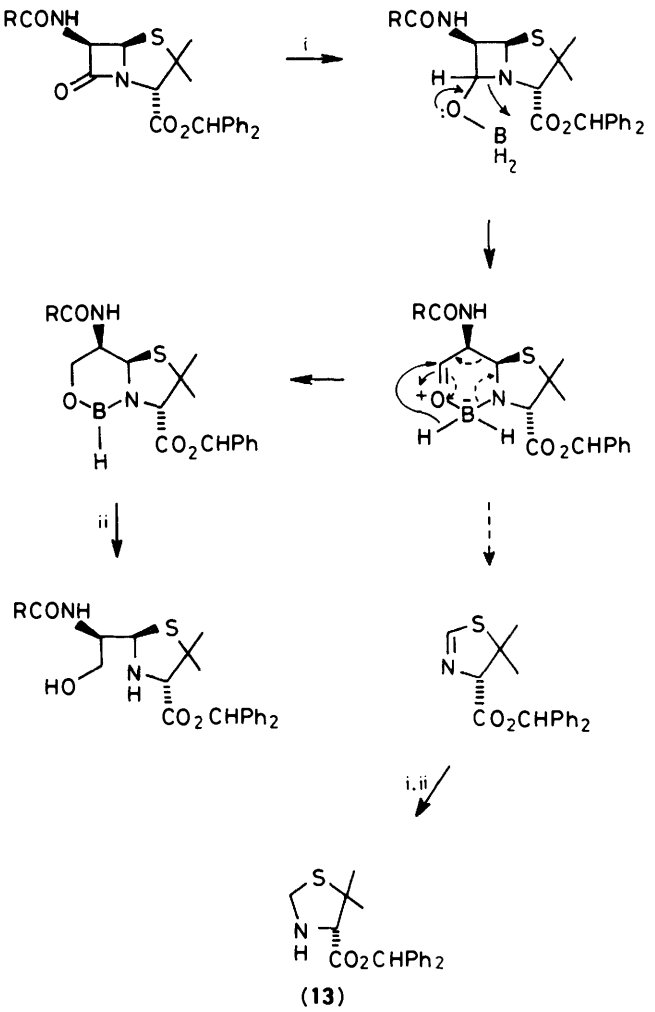


aminopenicillanic acid with benzyl chloroformate followed by esterification with diphenyldiazomethane.

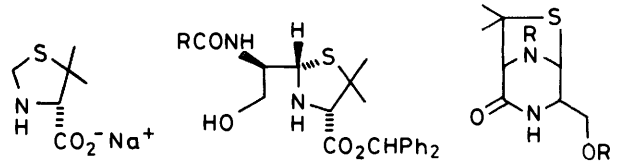
Reduction of the amide (**11**) with diborane afforded a major, more polar material and a minor, less polar material. The former product was identified as the amino alcohol (**12**) (35%). The less polar material was identified as benzhydryl 5,5-dimethylthiazolidine-4-carboxylate (**13**), formed in 25% yield. The thiazolidine (**13**) presumably arises by fragmentation of a reduction imtermediate, followed by further reduction (see Scheme 2). The ester (**13**) could be hydrolysed, using sodium hydroxide in aqueous dioxane, to give the sodium salt (**14**).

Having failed to observe the direct reduction of the β-lactam ring to an azetidine, the possibility of utilising the former moiety for the synthesis of the latter was investigated. Initially, the chemical behaviour of the amino alcohols was explored, particularly that of compound (**12**). Whilst compound (**12**) was relatively stable under neutral conditions, treatment with acid rapidly caused an equilibration to occur. Thus, on leaving (**12**) in deuteriochloroform for 2 days, a new pair of methyl signals appeared in the n.m.r. spectrum; examination of the mixture by t.l.c. showed two closely running spots, suggesting that equilibration to give a mixture of the C-2 epimers (**12**) and (**15**) had occurred; compound (**8**) behaved similarly, equilibrating with its epimer (**16**). Such behaviour has been observed in other β-lactam ring-opened products of penicillin.[6,7] The hydrochloride salts of compounds (**8**) and (**12**) were prepared by passing dry HCl gas into ether solutions. The hygroscopic precipitates were dissolved in methanol and their specific rotations measured; both the salts of compounds (**8**) and (**12**) showed mutarotation, falling to equilibrium values within 5 h (see Experimental section).

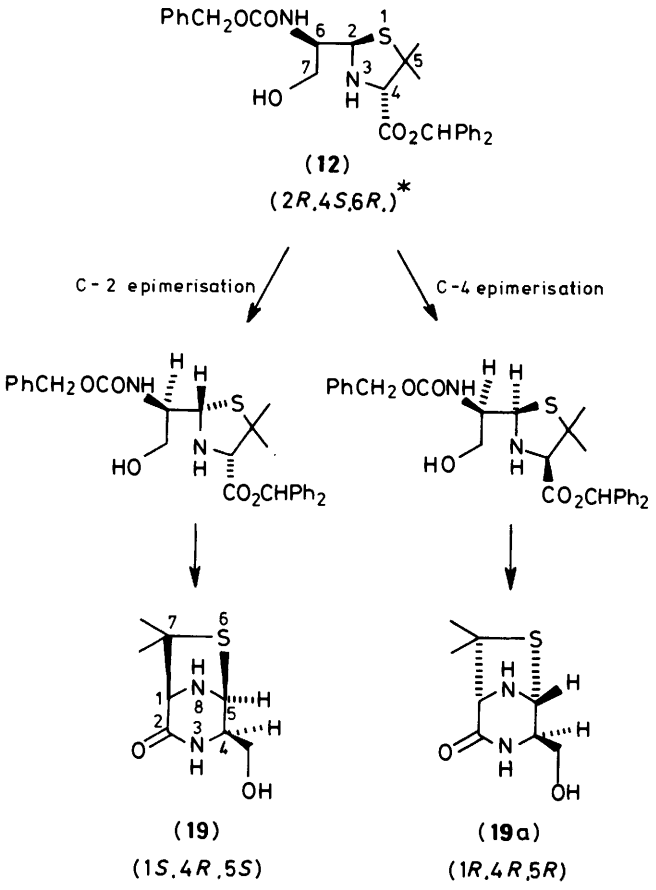
Treatment of the amino alcohol (**12**) with potassium hydroxide in methanol at room temperature afforded benzyl alcohol, benzhydrol, and two new products, one acidic and the other weakly basic. Neither of these products corresponded to the required azetidine. The less polar, weakly basic compound was isolated as a crystalline solid (31% yield), and analysed as $C_8H_{14}N_2O_2S$. The ^1H n.m.r., i.r., and mass spectra of this compound were consistent with the structure (**17**) (without defining its stereochemistry). Prolonged acetylation of this material afforded the diacetyl derivative (**18**), which was shown by ^1H n.m.r. spectroscopy to contain acylated alcohol and



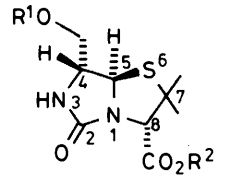
Scheme 2. *Reagents:* i, B_2H_6; ii, H_3O^+



amine functions. Assuming the starting alcohol (**12**) has the same stereochemistry at positions 2, 4, and 6 as in the starting penicillin (**11**), it is necessary to invoke an epimerisation at either C-2 or C-4 in order to account for the intramolecular cyclisation yielding compound (**17**) (Scheme 3). The configuration (*R*) about position 6 would not be expected to change; epimerisation at positions 2 and 4 would lead to the alternative isomers (**19**) and (**19a**) respectively. Molecular models indicate for compound (**19**) a dihedral angle between 4- and 5-H of *ca.* 50 ± 5° resulting in a coupling constant in the region 2.5—3.5 Hz. For compound (**19a**), the dihedral angle is 80 ± 5°, indicating an expected coupling constant in the range 0.5—1.5 Hz. The observed coupling constant of 2.7 Hz supports structure (**19**), resulting from epimerisation about position 2 of the amino alcohol (**12**). Rearrangements related to the process (**12**)→(**19**) have been observed in the penicillin field.[8]

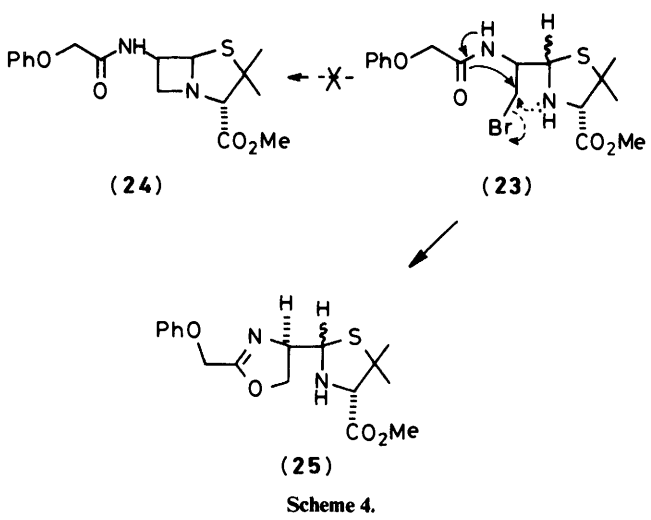


Scheme 3.* The non-systematic numbering scheme shown in structure (**12**) is that used for the n.m.r. assignments

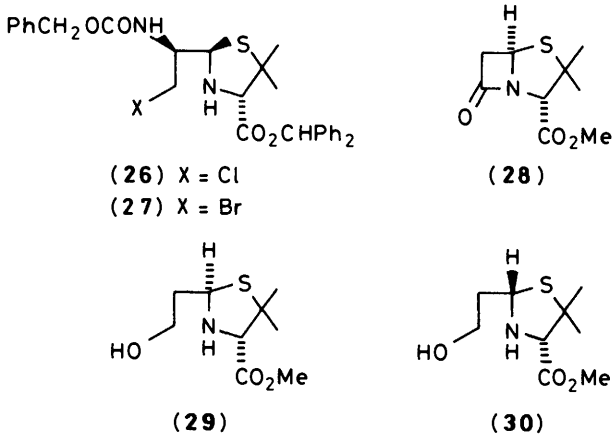


(**20**) $R^1 = R^2 = H$
(**21**) $R^1 = Ac$, $R^2 = H$
(**22**) $R^1 = Ac$, $R^2 = Me$

The more polar, acidic product from the reaction of compound (**12**) with methanolic potassium hydroxide exhibited the two signals arising from 1- and 4-H in (**12**) at lower fields than those in compound (**19**) and it analysed as $C_9H_{14}N_2O_4S$, suggesting retention of the carbonyl carbon of the urethane function. This product was assigned as the fused thiazolidine (**20**). Acetylation gave a monoacetate (**21**), the n.m.r. shifts being consistent with acylation of a hydroxymethyl group; the acetate (**21**) formed a methyl ester (**22**) with diazomethane. The stereochemistry at C-4 is expected to be (*R*), as in the starting material. The configuration at C-8 is difficult to assign with certainty; however, since only one isomer of this constitution was formed, we assumed that this has not changed. The two C-5 epimers may be distinguished by the 4-H to 5-H coupling constant; for retention of the configuration (5*R*) about this point the dihedral angle between these protons would be *ca.* 120°, requiring a *J* value of *ca.* 2 Hz; in the (5*S*)-epimer the protons are eclipsed, for which a *J* value of *ca.* 8 Hz would be



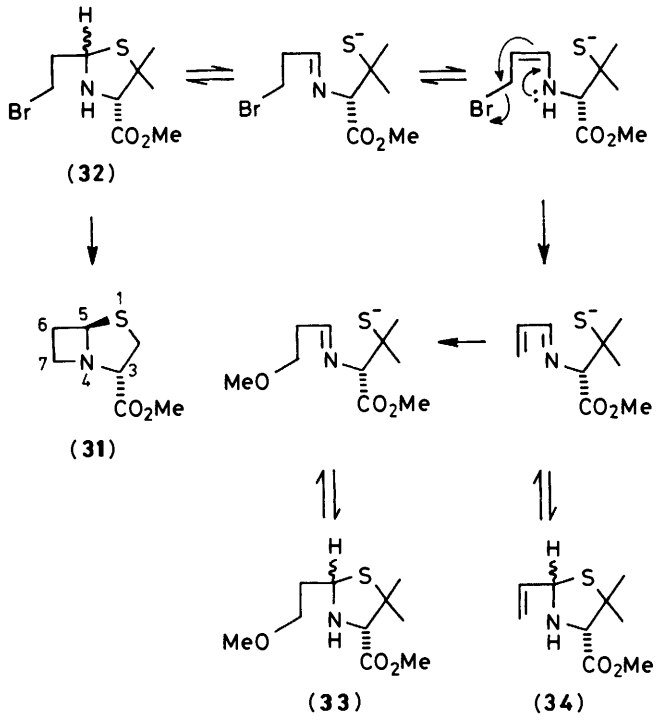
Scheme 4.



expected. The observed $J_{4,5}$ of 1.4 Hz therefore suggests retention of configuration at position 5. Compounds related to structure (**20**) are known;[7,9,10] in independent work, Petursson and Waley have observed similar reactions for compounds related to the amino alcohol (**12**).[11]

Attention was next directed towards the cyclisation of the amino alcohols using the methods we have recently described.[12] Because of the highly functionalised nature of the bromo amines, *e.g.* (**23**), interference from the acylamido function was expected to give compounds of the type (**25**) when attempting the cyclisation of amino alcohol derivatives such as (**23**) (Scheme 4). These derivatives may be prepared from the alcohols by reaction with reagents such as triphenylphosphine in either carbon tetrachloride[13] or carbon tetrabromide.[14] Indeed, treatment of the amino bromide (**23**) with sodium methoxide in methanol afforded, as the major product, the dihydro-oxazole (**25**) rather than the azetidine (**24**). The dihydro-oxazole (**25**) gave in its mass spectrum, in the major fragmentation process, the ion (**10**; R = Me) corresponding to cleavage of the 2,10-bond. A similar result was obtained starting with the amino alcohol (**12**) and its desired chloride (**26**) and bromide (**27**).

Because of these chemical side-reactions, studies on the unsubstituted penicillanic acid were made. The reduction of methyl penicillanate (**28**)[15] with diborane gave the expected amino alcohol (**29**), together with its epimer (**30**); epimerisation about position 2 appears to be particularly easy in this series. Cyclisation of the amino alcohol (**29**), either alone or as a

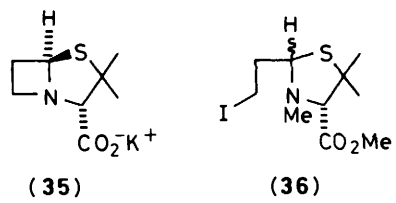


Scheme 5.

mixture with its epimer (**30**), could be effected under two sets of conditions. In the first method the alcohol (**29**) was treated with boron trifluoride–ether, followed by triphenylphosphine and diethyl azodicarboxylate for 2 days[12] to afford, as the major product, the desired acetidine (**31**) (30% yield). Alternatively, the azetidine (**31**) could be prepared by a two-step process. Reaction of the mixture of amino alcohols (**29**) and (**30**) with triphenylphosphine and carbon tetrabromide gave the bromide (**32**), again as an epimeric mixture. Of the methods used to effect the cyclisation of the bromo amide (**32**), sodium methoxide in refluxing methanol proved most productive, forming the azetidine (**31**) in 12% yield. Two other products were also isolated from the latter reaction; the first proved to be the methoxy derivative (**33**), as an epimeric mixture, and the second the vinylic system (**34**). Further treatment of the unsaturated compound with sodium methoxide in methanol gave the methoxy adduct (**33**). Presumably the latter compounds form by ring-opening of the bromo amide, with elimination of bromide followed by recyclisation or conjugate addition of methanol prior to recyclisation (Scheme 5). The azetidine (**31**) was unaffected by further treatment with base.

Only one epimer of the azetidine was isolated. That this had the configuration depicted followed from n.O.e. difference experiments; irradiation of 3-H caused enhancement of the 2β-methyl group, while irradiation of the 2α-methyl group caused enhancement of 5-H, indicating a *trans*-relationship between 3- and 5-H. Since the azetidine retained the optical activity, the product must have the absolute configuration shown. The two bromide epimers (**32**) could only be separated with difficulty, and therefore the origin of the azetidine (**31**) from one or both of the epimers cannot be distinguished; it is likely, however, that during the base-catalysed process only the (2*R*)-epimer reacts to form the azetidine (**31**), the (2*S*)-epimer probably reacting by ring-opening to give products of the type (**33**) and (**34**).

Treatment of the azetidine ester (**31**) with potassium hydroxide (1 equiv.) afforded the corresponding potassium salt



(**35**), which could be reconverted into the methyl ester by acidification and treatment with diazomethane.

The azetidine (**31**) was stable to strong bases but reacted smoothly with alkylating agents such as methyl iodide to give ring-opened products, including the iodo compounds (**36**). The azetidine was also sensitive to acid, treatment with toluene-*p*-sulphonic acid in methanol generating the methoxy compounds (**33**).

The potassium salt (**35**) proved to be a very weak β-lactamase inhibitor,* indicating the need for the acylamide side-chain as an extra binding site for the enzyme.

Experimental

M.p.s were recorded on a hot-stage apparatus and are uncorrected. I.r. spectra were obtained on various Perkin-Elmer spectrophotometers using chloroform solutions unless otherwise specified. ^{1}H N.m.r. spectra were recorded on a Varian EM360A (60 MHz), Perkin-Elmer R32, or JEOL FX90Q (90 MHz) instrument and are quoted in p.p.m. relative to tetramethylsilane as internal standard using deuteriochloroform as solvent unless otherwise stated; high-field (400 MHz) spectra were obtained *via* the S.E.R.C. service of the University of Sheffield. ^{13}C N.m.r. spectra were recorded on the JEOL FX90Q instrument. Optical rotation measurements were obtained on a Thorn NPL 243 automatic polarimeter. Accurate mass measurements were performed on a Kratos A.E.I. MS9 50 with instrument operated in the E.I. mode. Salts were mixed with NH_4Cl before ionization.

Thin-layer chromatography (t.l.c.) was performed either on aluminium plates pre-coated with Merck Kieselgel (0.2 mm) or on glass plates coated before use with Merck Kieselgel $60GF_{254}$. Acidic products were eluted with the solvent system ethyl acetate–methanol–acetic acid (50:10:1). Preparative-layer chromatography (p.l.c.) was performed using 20 × 20 cm plates coated with 1 mm of Kieselgel $60GF_{254}$, and for column chromatography Merck Kieselgel 60G or LiChroprep Si60 was employed. Solvents were generally of SLR grade and were purified and dried as necessary by standard methods. Solvents for chromatography were distilled before use. Light petroleum refers to the fraction of boiling range 60—80 °C; THF denotes tetrahydrofuran, and ether refers to diethyl ether. Reactions involving oxygen or water-sensitive materials were routinely performed under oxygen-free dry nitrogen. Extracts were dried over anhydrous sodium sulphate and acidifications were performed using 10% orthophosphoric acid solution.

Esters of penicillin V were prepared by standard methods, using the reaction of the free acid with the appropriate diazoalkane.[5]

Benzhydryl (2R,4S)-2-[(1R)-2-*Hydroxy*-1-*phenoxyacetylamino*)*ethyl*]-5,5-*dimethylthiazolidine*-4-*carboxylate* (**8**).—Benzhydryl (3*S*,5*R*,6*R*)-6-phenoxyacetylaminopenicillanate (**6**) (1.55 g, 3 mmol) was dissolved in THF (50 ml), stirred and cooled to −10 °C. Diborane gas was generated externally by

*We thank Dr. S. G. Waley, Sir William Dunn School of Pathology, University of Oxford, for these biological assays.

the addition of sodium borohydride (0.103 g, 2.7 mmol) in diglyme to boron trifluoride–ether (0.75 g, 5.3 mmol) in diglyme. The diborane gas was passed into the reaction vessel with the aid of a slow stream of nitrogen. The solution was stirred for 4 h at −10 °C and then at room temperature overnight. Saturated aqueous ammonium chloride was added, the mixture was extracted with ether, and the extracts were dried and evaporated. Chromatography (60 g SiO_2, 1:1 EtOAc–light petroleum) gave three fractions. The first showed $\nu_{max.}$ 2 380 (B–H) and 1 740 cm^{-1} and no secondary amide band; this material is probably boron-complexed over-reduction products. The second fraction was unreduced starting material (24%). The more polar fraction was identified as the *title amino alcohol* (0.37 g, 24%), isolated as a non-crystalline solid, $[\alpha]_D^{19}$ +63° (*c* 0.85, $CHCl_3$); $\nu_{max.}$ 3 405, 3 340, 1 735, and 1 672 cm^{-1}; δ 0.96 (3 H, s, Me), 1.52 (3 H, s, Me), 3.30 (2 H, br s, exch. D_2O, OH and NH), 3.6—3.9 (4 H, m), 4.50 (2 H, s, PhOCH_2), 4.82 (1 H, d, *J* 6 Hz, 2-H), and 6.8—7.5 (16 H, m); *m/z* 502 (M^+ −18), 391, 326, 167, 94, and 52 (Found: C, 66.5; H, 6.3; N, 5.3; S, 6.1. $C_{29}H_{32}N_2O_5S$ requires C, 66.9; H, 6.2; N, 5.4; S, 6.2%).

Benzhydryl (2R,4S)-2-[(1R)-2-*Acetoxy*-1-*phenoxyacetylaminoethyl*]-5,5-*dimethylthiazolidine*-4-*carboxylate* (**9**).—The amino alcohol (**8**) (50 mg) was stirred overnight, at room temperature, with pyridine (1 ml) and acetic anhydride (1 ml). EtOAc was added and the solution washed copiously with water, dried, and evaporated. The residue was purified by p.l.c. (EtOAc–light petroleum, 1:1) giving the *title monoacetate* (46 mg, 85%) as a glassy solid, $\nu_{max.}$ 1 735 and 1 680 cm^{-1}; δ 0.97 (3 H, s, Me), 1.51 (3 H, s, Me), 2.00 (3 H, s, MeCO), 3.37 (1 H, m, exch. D_2O, ring NH), 3.77 (1 H, s, 4-H), 4.1—4.3 (3 H m), 4.53 (2 H, s, PhOCH_2), 4.78 (1 H, d, *J* 6 Hz, 2-H), and 6.8—7.4 (16 H, m); *m/z* 502 (M^+ − AcOH), 391, 326, 291, 258, 167, and 94 (Found: C, 65.6; H, 5.9; N, 4.9. $C_{31}H_{34}N_2O_6S$ requires C, 66.2; H, 6.0; N, 5.0%).

Benzhydryl (3S,5R,6R)-6-*Benzyloxycarbonylaminopenicillanate* (**11**).—6-Aminopenicillanic acid (7.3 g, 33.7 mmol) was dissolved in water (50 ml) containing sodium hydroxide (1.35 g, 33.7 mmol) at 0 °C with stirring. To the clear solution was added sodium hydrogen carbonate (3 g, 36 mmol) followed, dropwise, by 95% benzyl chloroformate (6.3 g, 35 mmol) during 40 min, the temperature being maintained between 0—10 °C. After a further 30 min at this temperature the solution was stirred for 2 h at room temperature, then washed with ether, acidified to pH 2—3, extracted with chloroform and the extracts washed with saturated brine, dried, and the solvent removed to give the 6-benzyloxycarbonylaminopenicillanic acid (10.7 g) as a foam. The acid (10.2 g) was dissolved in dichloromethane, and cooled in ice as a solution of diphenyldiazomethane in hexane was added. After 2 h, decolourisation and nitrogen evolution had almost ceased. The solution was then washed with aqueous sodium hydrogen carbonate, dried, filtered and evaporated, giving the crude product which was purified by chromatography (280 g, SiO_2, 3:7, EtOAc–light petroleum) to afford the *title compound* (10.9 g, 74%). An analytical sample was obtained by p.l.c.; isolated as a solid foam this showed $[\alpha]_D^{21}$ +127° (*c* 0.28, $CHCl_3$), $\nu_{max.}$ 1 782, 1 725 cm^{-1}; δ 1.23 (3 H, s, Me), 1.55 (3 H, s, Me), 4.52 (1 H, s, 3-H), 5.10 (2 H, s, PhCH_2), 5.4—5.7 (2 H, m), 6.95 (1 H, s, Ph_2CH), and 7.3 (15 H, aromatic H) (Found: C, 67.3; H, 5.4; N, 5.4; S, 6.5. $C_{29}H_{28}N_2O_5S$ requires C, 67.4; H, 5.4; N, 5.4; S, 6.2%).

Reduction of the Benzyloxycarbonamide (**11**).—The ester (**11**) (8.5 g, 16.5 mmol) in dry THF (200 ml) was treated with diborane, generated by adding a solution of sodium borohydride (0.85 g, 22.3 mmol) in diglyme to boron trifluoride–ether (5.3 g, 37 mmol) in diglyme. After 4 h at −10 °C the solution was stirred at room temperature overnight. A further quantity of diborane, using half the above amounts of precursors was added, and the solution was stirred for a further 6 h before addition of aqueous ammonium chloride solution and ether extraction. The crude product was chromatographed through silica gel (240 g, EtOAc–light petroleum, 1:3 rising to 2:3), yielding, as the major product, *benzhydryl* (2R,4S)-2-[(1R)-1-*benzyloxycarbonylamino*-2-*hydroxyethyl*]-5,5-*dimethylthiazolidine*-4-*carboxylate* (**12**) (3.0 g, 35%) as a foam. A sample was further purified, by p.l.c., to give crystals, m.p. 102—107 °C, $[\alpha]_D^{20}$ +88° (*c* 0.66, $CHCl_3$), $\nu_{max.}$ 3 425, 3 345, 1 730, and 1 720 cm^{-1}; δ (400 MHz) 0.96 (3 H, s, Me), 1.52 (3 H, s, Me), 1.85 (1 H, br s, exch. D_2O, OH), 3.12 (1 H, br s, exch. D_2O, NH), 3.61 (1 H, s, 6-H), 3.71 (1 H, dd, *J* 4, 12 Hz, CH_2OH), 3.76 (1 H, dd, *J* 4, 12 Hz, CH_2OH), 3.79 (1 H, s, 4-H), 4.77 (1 H, d, *J* 7 Hz, 2-H), 5.08 (2 H, s, PhCH_2), 5.77 (1 H, br s, CONH), 6.93 (1 H, s, Ph_2CH), and 7.32 (15 H, m, aromatic H); δ_C(p.p.m.) 26.82, 27.57, 57.64, 59.05, 62.73, 65.88, 67.07, 72.11, 78.39, 156.84, and 168.97; *m/z* 502 (M^+ − H_2O), 291, 245, 217, 167, and 91 (Found: C, 66.5; H, 6.3; N, 5.4; S, 6.3. $C_{29}H_{32}N_2O_5S$ requires C, 66.9; H, 6.2; N, 5.4; S, 6.2%).

A less polar product, isolated from the column chromatography, was *benzhydryl* (4S)-5,5-*dimethylthiazolidine*-4-*carboxylate* (**13**) (1.32 g, 25%). An analytical sample was obtained by sublimation to give m.p. 108—113 °C, $\nu_{max.}$ 1 727 cm^{-1}; δ 1.01 (3 H, s, Me), 1.64 (3 H, s, Me), 2.70 (1 H, br s, exch. with D_2O, NH), 3.59 (1 H, s, 4-H), 4.20 (1 H, d, *J* 10 Hz, 2-H), 4.30 (1 H, d, *J* 10 Hz, 2-H), 6.99 (1 H, s, Ph_2CH), and 7.31 (10 H, m, aromatic H) (Found: C, 69.9; H, 6.4; N, 4.4; S, 9.6. $C_{19}H_{21}NO_2S$ requires C, 69.7; H, 6.4; N, 4.3; S, 9.8%).

Sodium (4S)-5,5-*Dimethylthiazolidine*-4-*carboxylate* (**14**).—The benzhydryl ester (**13**) (0.16 g, 0.5 mmol) in dioxane (3 ml) was treated with sodium hydroxide (30 mg, 0.75 mmol) in water (0.5 ml), and then stirred overnight. Much of the solvent was then evaporated, EtOAc and water were added, the organic phase was dried and the solvent removed, yielding benzhydrol, m.p. 65—67 °C (lit.,[16] m.p. 69 °C). The aqueous phase was also evaporated to dryness, taken up in methanol, adjusted to pH 7.5 by careful addition of methanolic HCl, filtered and evaporated to give the title compound (**14**), m.p. >230 °C (decomp.), δ(CD_3OD) 4.23 (1 H, d, *J* 9 Hz, 2-H), 4.03 (1 H, d, *J* 9 Hz, 2-H), 3.32 (1 H, s, 4-H), 1.63 (3 H, s, Me), and 1.27 (3 H, s, Me); *m/z* 184 (M^+ + H^+), 161 (M^+ − Na), 116, 105, 87, 75, and 69.

Treatment of the Amino Alcohols (**8**) *and* (**12**) *with Acid.*—The amino alcohol (**8**) (97 mg, 0.19 mmol) in ether (2 ml) was treated with HCl gas, producing the hydrochloride as a white precipitate. The ether was decanted and the solid washed twice with ether and dried. The resulting white powder could not be crystallised from ethanol–ether mixtures. The solid had $[\alpha]_D^{22}$ (initial) +58.8→+38.7° (after 5 h) (*c* 1.09, MeOH); δ(initial, CD_3OD) 1.22 (3 H, s, Me), 1.68 (3 H, s, Me), 4.00 (4 H, m, 6-H, 7-H_2, 4-H), 4.60 (2 H, s, PhOCH_2), 5.17 (1 H, d, *J* 7 Hz, 2-H), and 6.9—7.5 (16 H, m, aromatic H and Ph_2CH). At equilibrium (4 h), the hydrochloride showed the following new peaks due to the presence of the 2-epimer: δ 1.15 (3 H, s, Me), 1.72 (3 H, s, Me), and 5.30 (1 H, d, *J* 5 Hz, 2-H); ratio initial:new *ca.* 2:3.

The amino alcohol (**12**) (0.5 g, 0.96 mmol) in dry ether was treated with ethereal hydrogen chloride, the ether decanted, and the residue washed with ether and dried to afford the hydrochloride as a non-crystalline powder (0.49 g, 88%), $[\alpha]_D^{20}$ +84→+54° (after 5 h) (*c* 0.55, MeOH); δ(CD_3OD) (initial) 1.25 (3 H, s, Me), 1.70 (3 H, s, Me), 3.70—4.10 (4 H, m, 6-H, 7-H_2, 4-H), 5.10 (1 H, d, 2-H), 5.13 (2 H, s, PhCH_2), 7.09 (1 H, s, Ph_2CH), and 7.30—7.55 (15 H, aromatic H).

Treatment of the Amino alcohol (**12**) *with Potassium Hydroxide*.—The amino alcohol (**12**) (1.94 g, 3.7 mmol) in methanol (30 ml) was stirred with a solution of potassium hydroxide (85%, 0.53 g, 8.0 mmol) in methanol (10 ml) at room temperature for 7 h. A small amount of solid carbon dioxide was added to the solution before removal of the solvent. The residual gum was triturated with ether and the residue (1.17 g) dissolved in water before extraction with EtOAc (×4). From the organic phase was obtained, after drying and removal of the solvent, (1S,4R,5S)-4-*hydroxymethyl*-7,7-*dimethyl*-2-*oxo*-3,8-*diaza*-6-*thiabicyclo*[3.2.1]*octane* (**19**) (0.13 g, 31%), m.p. (EtOAc–light petroleum) 189—192 °C, $\nu_{max.}$ 3 380, 3 320, and 1 670 cm^{-1}; δ(CD_3OD) 1.45 (3 H, s, Me), 1.52 (3 H, s, Me), 3.44 (1 H, s, 1-H), 3.5—3.9 (3 H, complex m, 4-H and CH_2OH), and 5.05 (1 H, d, *J* 2.7 Hz, 5-H); *m/z* 202 (M^+), 184, 128, 110, 97, 83, 69, and 59 (Found: *m/z* 202.0768; C, 47.8; H, 7.0; N, 13.7. $C_8H_{14}N_2O_2S$ requires *m/z* 202.0776; C, 47.5; H, 7.0; N, 13.8%).

The aqueous extract was treated with ion exchange resin (Dowex 50W-X8, H^+ form), then methanol was added and the mixture filtered. The solution was evaporated to dryness and triturated with methanol. The alcoholic solution gave, upon evaporation, (4R,5R,8S)-4-*hydroxymethyl*-7,7-*dimethyl*-2-*oxo*-1,3-*diaza*-6-*thiabicyclo*[3.3.0]*octane*-8-*carboxylic acid* (**20**) (0.08 g, 17%) as a non-crystalline solid, δ(CD_3OD) 1.54 (3 H, s, Me), 1.57 (3 H, s, Me), 3.5—3.8 (3 H, m, 4-H and CH_2OH), 4.49 (1 H, s, 8-H), and 5.42 (1 H, d, *J* 1.4 Hz, 5-H); *m/z* 246 (M^+), 228, 184, 169, 129, 82, 69, and 55 (Found: *m/z* 246.0672. $C_9H_{14}N_2O_4S$ requires *M*, 246.0674).

Acetylation of the alcohol (**20**) (8 mg) with acetic anhydride in pyridine, in the normal manner, afforded the *monoacetate* (**21**), $\nu_{max.}$ 1 720 cm^{-1}; δ 1.59 (6 H, s, Me_2C), 2.10 (3 H, s, MeCO), 3.9—4.2 (3 H, m, 4-H, CH_2OAc), 4.62 (1 H, s, 8-H), 5.40 (1 H, d, *J* 1.5 Hz, 5-H), and 6.26 (2 H, s, exch. with D_2O, CO_2H, NH); *m/z* 184 (M^+, $-AcOH - CO_2$), 150, 114, 97, 82, 69, and 55. This acetate was methylated, with diazomethane in ether–dichloromethane, and the product purified by t.l.c. The *methyl ester* (**22**) showed *m/z* 302 (M^+) 242 ($M^+ - AcOH$), 174, 168, 128, 114, 97, 83, 69, and 59 (Found: *m/z* 302.0929. $C_{12}H_{18}N_2O_5S$ requires *M*, 302.0936).

Acetylation of the Alcohol (**19**).—The alcohol (15 mg) was dissolved in pyridine (1 ml) and treated with acetic anhydride (0.2 ml) at room temperature for 5 h. Evaporation of the reagents afforded a product which, after p.l.c., provided (1S,4R,5S)-4-*acetoxymethyl*-8-*acetyl*-7,7-*dimethyl*-2-*oxo*-3,8-*diaza*-6-*thiabicyclo*[3.2.1]*octane* (**18**), as an amorphous solid, $\nu_{max.}$ 3 380, 1 741, and 1 675 cm^{-1}; δ 1.49 (3 H, s, Me), 1.59 (3 H, s, Me), 2.09 (3 H, s, MeCO), 2.16 (3 H, s, MeCO), 3.9—4.25 (4 H, m, 1-, 4-H, CH_2OAc), 6.08 (1 H, d, *J* 1.8 Hz, 5-H), and 6.26 (1 H, s, exch. D_2O, NH); *m/z* 286 (M^+), 226, 185, 151, 110, 97, 83, 69, and 55 (Found: *m/z* 286.0982. $C_{12}H_{18}N_2O_4S$ requires *M*, 286.0987).

Formation of the Bromides (**23**).—Methyl 6β-phenoxyacetamidopenicillanate (10.6 g, 29 mmol) was reduced by diborane in the same manner as described for the corresponding benzhydryl ester (*vide supra*) to produce the corresponding *amino alcohol* (3.52 g, 33%), $\nu_{max.}$ 1 750, 1 680 cm^{-1}; δ 1.2 (3 H, s, Me), 1.57 (3 H, s, Me), 3.2—3.6 (2 H, m, NH and OH), 3.7 (1 H, s, 4-H), 3.77 (3 H, s, CO_2Me), 3.8—3.83 (2 H, m), 3.9 (1 H, m, 6-H), 4.54 (2 H, s, OCH_2CO), 4.82 (1 H, d, *J* 7 Hz, 2-H), and 7.3—7.9 (6 H, m, Ph and CONH) (Found: M^+, 369.148 40. $C_{17}H_{25}N_2O_5S$ requires *M*, 269.148 41).

The alcohol (0.2 g, 0.5 mmol) in dry acetonitrile (6 ml) was stirred under nitrogen at 0 °C and then triphenylphosphine (0.16 g) and carbon tetrabromide (0.21 g) were added. The temperature was allowed to reach room temperature and stirring continued overnight before removing the solvent under reduced pressure. Column chromatography afforded the two epimeric bromides (**23**). The less polar isomer (88 mg, 43%) showed $[\alpha]_D^{23}$ +34.5° (*c* 0.74, $CHCl_3$), $\nu_{max.}$ 1 740 and 1 670 cm^{-1} [Found: (M^+ − HBr) 350.130 14. $C_{17}H_{12}N_2O_4S$ requires 350,130 02]. The more polar isomer (54 mg, 27%) showed $[\alpha]_D^{23}$ + 1.8° (*c* 0.56, $CHCl_3$), $\nu_{max.}$ 1 740, 1 680 cm^{-1} [Found: (M^+ − HBr) 350,130 39. $C_{17}H_{22}N_2O_4S$ requires 350.130 02].

Formation of Methyl 5,5-*Dimethyl*-2-(2-*phenoxy*-4,5-*dihydro*-1,3-*oxazol*-4-*yl*)*thiazolidine*-4-*carboxylate* (**25**).—The bromide mixture (**23**) (1.2 g, 2.76 mmol) in dry methanol (60 ml) at room temperature was treated with sodium methoxide (1.2 equiv.) in methanol (8 ml) and the mixture stirred for 25 h at room temperature, after which time the solvent was removed under reduced pressure. Ether (200 ml) was added and the mixture washed with brine (70 ml), dried ($MgSO_4$), and evaporated. Column chromatography of the residue over silica, using 7:3 ethyl acetate–light petroleum as eluant, gave the *dihydro-oxazole* (**25**) (0.58 g, 60%), $[\alpha]_D^{18}$ +43° (*c* 1.74, $CHCl_3$), $\nu_{max.}$ 1 740 and 1 670 cm^{-1}; δ 1.18 (3 H, s, Me), 1.63 (3 H, s, Me), 3.63 (1 H, s, 4-H), 3.77 (3 H, s, CO_2Me), 4.1 (1 H, dd, *J* 9 Hz, 7-H), 4.43 (1 H, dd, *J* 9, 10 Hz, 7-H), 4.56 (1 H, d, *J* 13 Hz, NH), 4.59—4.65 (1 H, m, 6-H), 4.7—4.8 (2 H, m, $PhOCH_2$), 4.82 (1 H, d, *J* 5 Hz, 2-H), 6.9—7.0 (3 H, m, aromatic H), and 7.2—7.35 (2 H, m, aromatic H) (Found: M^+, 350.129 68. $C_{17}H_{22}N_2O_4S$ requires *M*, 350.130 02).

Benzhydryl (2R,4S)-2-[(1S)-1-*Benzyloxycarbonylamino*-2-*chloroethyl*]-5,5-*dimethylthiazolidine*-4-*carboxylate* (**26**).—The alcohol (**12**) (0.26 g, 0.5 mmol) in dry acetonitrile (6 ml) was treated with triphenylphosphine (0.26 g, 1.0 mmol), triethylamine (0.14 g, 1.5 mmol), and carbon tetrachloride (0.16 g, 1.0 mmol). The solution was stirred at room temperature for 16 h, the mixture was evaporated to dryness, and the residue was chromatographed on silica (20 g), eluting with 1:4 EtOAc–light petroleum, to give the *title chloride* (**26**) (0.15 g, 55%) as a colourless foam, $[\alpha]_D^{20}$ +74° (*c* 0.43, $CHCl_3$), $\nu_{max.}$ 3 410, 3 340, and 1 712 cm^{-1}; δ 0.98 (3 H, s, Me), 1.56 (3 H, s, Me), 3.45 (1 H, br s, exch. D_2O, NH), 3.6—4.1 (4 H, m, CH_2Cl, 4-, 6-H), 4.81 (1 H, d, *J* 7 Hz, 2-H), 5.09 (2 H, s, $PhCH_2$), 5.25 (1 H, br d, *J* 9 Hz, CONH), 6.97 (1 H, s, Ph_2CH), and 7.31 (15 H, br s, aromatic H) (Found: C, 64.5; H, 5.8; Cl, 6.6; N, 5.2. $C_{29}H_{31}ClN_2O_4S$ requires C, 64.6; H, 5.8; Cl, 6.6; N, 5.2%).

Benzhydryl (2R,4S)-2-[(1S)-*Benzyloxycarbonylamino*-2-*bromoethyl*]-5,5-*dimethylthiazolidine*-4-*carboxylate* (**27**).—The alcohol (**12**) (0.52 g, 1.0 mmol), triphenylphosphine (0.4 g, 1.5 mmol), and carbon tetrabromide (0.5 g, 1.5 mmol) were stirred in dry acetonitrile (10 ml) and triethylamine (0.2 g, 2 mmol) at room temperature for 2 h. The solvent was removed under reduced pressure and the residue chromatographed through silica (45 g), using 1:5 EtOAc–light petroleum as eluant, to give the *title bromide* (0.36 g, 62%) as a colourless foam $[\alpha]_D^{20}$ +69° (*c* 0.25, $CHCl_3$), $\nu_{max.}$ 3 400, 3 335, and 1 715 cm^{-1}; δ (400 MHz) 0.98 (3 H, s, Me), 1.57 (3 H, s, Me), 3.42 (1 H, br s, exch. D_2O, NH), 3.61 (1 H, dd, *J* 3.5, 11 Hz, CH_2Br), 3.72 (1 H, dd, *J* 3.5, 11 Hz, CH_2Br), 3.84 (2 H, m, 4- and 6-H), 4.78 (1 H, d, *J* 7 Hz, 2-H), 5.09 (2 H, s, $PhCH_2$), 5.24 (1 H, d, *J* 8 Hz, CONH), 6.95 (1 H, s, Ph_2CH), and 7.32 (15 H, s, aromatic H); *m/z* 326, 291, 167, 105, and 91 (Found: C, 59.9; H, 5.3; Br, 13.8; N, 4.7. $C_{29}H_{31}BrN_2O_4S$ requires C, 59.7; H, 5.3, Br, 13.7; N, 4.8%).

Reduction of Methyl Penicillanate (**28**).—The ester (1 g, 4.6 mmol) in dry THF (35 ml) was treated at −10 °C with diborane gas, generated by the addition of sodium borohydride (0.16 g, 4.2 mmol) in diglyme to boron trifluoride–ether (0.99 g, 7 mmol) in diglyme. The mixture was stirred for 3 h at −10 °C and room temperature overnight. The mixture was then treated with a

saturated aqueous solution of ammonium chloride for 1 h before extraction with ether. The crude product showed two closely rising spots on t.l.c., shown to be the two isomers of the alcohol. The product was separated by chromatography through silica (50 g) using 3:2 EtOAc–light petroleum as eluant. The major product was *methyl* (2R,4S)-2-(*2-hydroxyethyl*)-*5,5-dimethylthiazolidine-4-carboxylate* (**29**) (0.52 g, 51%), m.p. 78—85 °C, $[\alpha]_D^{20}$ +57° (*c* 0.09, $CHCl_3$), $\nu_{max.}$(Nujol) 3 230 and 1 730 cm^{-1}; δ 1.18 (3 H, s, Me), 1.62 (3 H, s, Me), 1.6—2.2 (2 H, m, 6-H_2), 3.65—3.85 (3 H, m, 4-H and CH_2OH), 3.74 (3 H, s, OMe), and 4.79 (1 H, dd, *J* 5, 9.5 Hz, 2-H); *m/z* 219 (M^+), 174, 150, 145, 114, 86, and 59 (Found: C, 49.6; H, 7.8; N, 6.1. $C_9H_{17}NO_3S$ requires C, 49.3; H, 7.8; N, 6.4%).

The minor product was the (2S,4S)-*epimer* (**30**) (93 mg, 9%), m.p. 86—91 °C, $[\alpha]_D^{20}$ +36° (*c* 0.21, $CHCl_3$), $\nu_{max.}$(Nujol) 3 230 and 1 730 cm^{-1}; δ 1.22 (3 H, s, Me), 1.65 (3 H, s, Me), 2.07 (2 H, m, 6-H_2), 2.50 (2 H, br s, exch. D_2O, OH and NH), 3.60 (1 H, s, 4-H), 3.70—3.95 (2 H, m, CH_2OH), 3.75 (3 H, s, OMe), and 4.74 (1 H, t, *J* 6 Hz, 2-H).

Methyl (2RS,4S)-2-(*2-Bromoethyl*)-*5,5-dimethylthiazolidine-4-carboxylate* (**32**).—The mixture of amino alcohols (**29**) and (**30**) (0.33 g, 1.5 mmol) in dry acetonitrile (10 ml) was stirred at room temperature whilst triphenylphosphine (0.58 g, 2.2 mmol), carbon tetrabromide (0.74 g, 2.2 mmol) and, finally, triethylamine (0.3 g, 3 mmol) were added. An exothermic reaction occurred; after the reaction had subsided the mixture was stirred for a further 16 h, filtered and the filtrate evaporated to dryness and chromatographed through silica (10 g), using 3:7 EtOAc–light petroleum as eluant. The *title compound* (**32**) was obtained, as a mixture of two epimers (0.33 g, 78%), $\nu_{max.}$ 3 310 and 1 740 cm^{-1}, *m/z* 283, 281 (M^+), 224, 222, 207, 209, 174, 149, 147, 128, 114, 87, and 59 (Found: *m/z* 283.0065. $C_9H_{16}{}^{81}BrNO_2S$ requires *M*, 283.0066).

Treatment of the Bromides (**32**) *with Sodium Methoxide.*—The bromide epimers (**32**) (0.3 g, 1.1 mmol) in dry methanol (15 ml) under nitrogen were refluxed with freshly prepared sodium methoxide (0.11 g, 2.1 mmol) for 3 h. The solution was evaporated to small bulk under reduced pressure and the residue subjected to flash chromatography over silica, eluting with 1:1 EtOAc–light petroleum, to give three products: *methyl* (2RS,4S)-2-*vinyl*-*5,5-dimethylthiazolidine-4-carboxylate* (**34**) (54 mg, 25%), $\nu_{max.}$ 3 310, 2 920, and 1 745 cm^{-1}; δ 1.20 (3 H, s, Me), 1.65 (3 H, s, Me), 3.5—3.8 (4 H, m, 3-H and CO_2Me), 4.9—5.45 (3 H, m), and 5.7—6.1 (1 H, m) (Found: M^+, 201.081 99. $C_9H_{15}NO_2S$ requires M, 201.082 34). *Methyl* (2RS,4S)-2-(*2-methoxyethyl*)-*5,5-dimethylthiazolidine-4-carboxylate* (**33**) (87 mg, 37%), $\nu_{max.}$ 3 310, 2 920, and 1 745 cm^{-1}; δ 1.2 (3 H, s, Me), 1.65 (3 H, s, Me), 1.75—2.4 (2 H, m), 2.6 (1 H, m, NH), 3.0—4.0 (9 H, m, including CO_2Me and MeO), and 4.8 (1 H, m, 2-H) (Found: C, 51.6; H, 8.2%; M^+, 233.1083 35. $C_{10}H_{19}NO_3S$ requires C, 51.1; H, 8.2%; M^+, 233.108 65). *Methyl* 7-*deoxopenicillanate* (**31**) (22 mg, 10%), $[\alpha]_D^{23}$ +114.1° (*c* 0.26, $CHCl_3$), $\nu_{max.}$ 2 920 and 1 740 cm^{-1}; δ (400 MHz) 1.33 (3 H, s, Me), 1.72 (3 H, s, Me), 2.18 (1 H, m, 6-H), 2.80 (1 H, m, 6-H), 3.55 (1 H, m, 7-H), 3.59 (1 H, s, 3-H), 3.73 (3 H, s, CO_2Me), 3.95 (1 H, m, 7-H), and 5.43 (1 H, ddd, *J* 0.5, 2.7, 6.5 Hz, 5-H) (Found: M^+, 201.082 11. $C_9H_{15}NO_2S$ requires *M*, 201.082 34).

Cyclisation of the Amino Alcohols (**29**) *and* (**30**).—Diethyl azodicarboxylate (0.22 ml, 1.4 mmol) and triphenylphosphine (0.36 g, 1.4 mmol) were stirred under nitrogen in dry THF (5 ml) at room temperature for 10 min and then added, dropwise, to a premixed solution of the alcohols (0.25 g, 1.1 mmol) and boron trifluoride–ether (0.16 ml, 1.3 mmol) in tetrahydrofuran (15 ml) at 0 °C during 40 min. The mixture was stirred at room temperature for 4 days. Ether (100 ml) was added and the mixture washed with saturated aqueous sodium carbonate (2 × 30 ml), back-extracting with more ether (3 × 30 ml). The combined ether layers were washed with brine (30 ml), dried ($MgSO_4$), filtered and evaporated to give a crude product. Flash chromatography over silica, eluting with 2:1 EtOAc–light petroleum, gave the recovered alcohol (20 mg) together with the azetidine (**31**) (67 mg, 24%), identical with the material described above.

Potassium 7-Deoxopenicillanate (**35**).—The azetidine ester (**31**) (59 mg, 0.3 mmol) in THF (7 ml) was treated with potassium hydroxide (16.5 mg, 0.3 mmol) in water (0.9 ml) at room temperature for 20 h, then the solvents were removed under reduced pressure to give the title salt (66 mg, 100%), $\nu_{max.}$(Nujol) 1 600 cm^{-1}; δ(D_2O) 1.34 (3 H, s, Me), 1.72 (3 H, s, Me), 1.9—2.4 (1 H, m, 6-H), 2.4—2.9 (1 H, m, 6-H), 3.4—3.8 (2 H, m, 7-H_2), 3.53 (1 H, s, 3-H), and 5.34 (1 H, dd, *J* 3,2. 6.4 Hz, 5-H).

Remethylation of a sample of the acidified salt, using diazomethane, re-formed the methyl ester (**31**) (t.l.c. comparison).

Reaction of the Azetidine (**31**) *with Methanol.*—The azetidine (15 mg) in dry methanol (3 ml) was treated with toluene-*p*-sulphonic acid (1 mg), under nitrogen, for 6 h. The solvent was removed, ether (20 ml) was added, and the mixture was washed with saturated aqueous sodium carbonate (2 × 7 ml), back-washing with ether (2 × 7 ml). The combined ether layers were washed with brine (10 ml), dried, filtered and evaporated to give an oil. The mixture was chromatographed over silica, eluting with 3:1 EtOAc–light petroleum, to give a mixture of the methyl ether (**33**) (9 mg, 53%).

Reaction of the Azetidine (**31**) *with Methyl Iodide.*—The azetidine (20 mg, 0.1 mmol) in dimethylformamide (3 ml) was treated with sodium hydrogen carbonate (17 mg, 0.2 mmol) and methyl iodide (0.05 ml, 0.8 mmol) at room temperature for 19 h. Ether (20 ml) was added and the mixture washed with brine (2 × 7 ml), back-extracting with ether (3 × 10 ml). The ether extracts were combined, dried, filtered, and evaporated to give a yellow oil. Flash column chromatography, using 1:6 EtOAc–light petroleum as eluant, gave three fractions. The first was recovered acetidine (2 mg), followed by one of the epimers *methyl* 2-(*2-iodoethyl*)-*3,5,5-trimethylthiazolidine-4-carboxylate* (**36**) (17 mg, 55%), $[\alpha]_D^{13}$ +17.3° (*c* 0.16, $CHCl_3$), $\nu_{max.}$ 1 645 cm^{-1}; δ 1.33 (3 H, s, Me), 1.63 (3 H, s, Me), 2.1—2.4 (2 H, m, 6-H_2), 2.43 (3 H, s, NMe), 3.1—3.4 (2 H, m, 7-H_2), 3.59 (1 H, s, 4-H), 3.73 (3 H, s, CO_2Me), and 4.63 (1 H, dd, *J* 4, 7 Hz, 2-H) (Found: M^+, 343.010 13. $C_{10}H_{18}NO_2IS$ requires *M*, 343.010 5).

The most polar fraction was the other epimer of iodide (**36**), (3 mg, 10%), m.p. 55—58 °C, $[\alpha]_D^{23}$ +7.9° (*c* 0.1, $CHCl_3$), $\nu_{max.}$ 1 745 cm^{-1}; δ 1.36 (3 H, s, Me), 1.51 (3 H, s, Me), 2.0—2.5 (2 H, m, 6-H_2), 2.39 (3 H, s, NMe), 3.1—3.4 (2 H, m, 7-H_2), 3.25 (1 H, s, 4-H), 3.77 (3 H, s, CO_2Me), and 3.86 (1 H, dd, *J* 3.6, 7.3 Hz, 2-H) (Found: C, 35.1; H, 5.3; N, 3.8. $C_{10}H_{18}INO_2S$ requires C, 35.0; H, 5.3; N, 41%).

Similar products were obtained by treatment of the potassium salt (**35**) with methyl iodide under the above reaction conditions.

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